

Remarks

The December 21, 2010 Official Action and the references cited therein have been carefully reviewed. In view of the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset it is noted that a shortened statutory response period of three (3) months was set forth in the December 21, 2010 Official Action. Therefore, the initial due date for response was March 21, 2011. Accordingly, a petition for a 1 month extension is presented with this response, which is being filed within the one month extension period.

The Examiner has rejected claims 1, 4, 5, 8, and 15 under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent 5,356,633 (Woodle et al.) and Metselaar et al. (Arthritis and Rheumatism (2003) 48:2059-2066).

The Examiner has also rejected claims 2, 4, 6, 7, 9-14, and 57-61 under 35 U.S.C. §103(a) as allegedly unpatentable over Woodle et al. and Metselaar et al. in view of Omelyanenko et al. (J. Controlled Rel. (1998) 53:25-37) and Smolen et al. (Nat. Rev. (2003) 2:473-488).

Claims 1, 2, and 4-15 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Wang et al. (Bioconjugate Chem. (2003) 14:853-859) and Metselaar et al.

Lastly, the Examiner has rejected claims 57-61 under 35 U.S.C. §103(a) as allegedly unpatentable over Wang et al. and Metselaar et al. in view of Smolen et al. and Omelyanenko et al.

The foregoing rejections constitutes all of the grounds set forth in the December 21, 2010 Official Action for refusing the present application.

In accordance with the instant amendment, claim 67 has been added, which reads on the elected invention. Support for new claim 67 can be found throughout the application including, for example, in original claim 64 and at page 22, lines 12-17. No new matter has been introduced into this application by reason of any of the amendments presented

herewith.

In view of the reasons set forth in this response, Applicants respectfully submit that the 35 U.S.C. §103(a) rejections of claims 1, 2, 4-15, and 57-61, as set forth in the December 21, 2010 Official Action, cannot be maintained. These grounds of rejection are, therefore, respectfully traversed.

CLAIMS 1, 4, 5, 8, AND 15 ARE NOT RENDERED OBVIOUS BY WOODLE ET AL. AND METSELAAR ET AL.

The Examiner has rejected claims 1, 4, 5, 8, and 15 under 35 U.S.C. §103(a) as allegedly unpatentable over Woodle et al. and Metselaar et al. It is the Examiner's position that Woodle et al. "teach compositions comprising a hydrophilic biocompatible polymer, polyethylene glycol (PEG), in combination with anti-inflammatory agents, such as NSAIDs." The Examiner acknowledges that Woodle et al. do not disclose the anti-inflammatory glucocorticoids, but contends that it would have been obvious to a skilled artisan to replace the NSAIDs of Woodle et al. in view of the teachings of Metselaar et al. Applicants respectfully disagree with the Examiner's position.

Claim 1 of the instant application, from which claims 4, 5, 8, and 15 depend, recites that the anti-inflammatory therapeutic agent is linked to a water-soluble polymer. At page 21 (as well as at claims 4 and 14), the instant application recites that water-soluble polymers include, for example, HPMA copolymer, polyethylene glycol, polyglutamic acid, polyaspartic acid, dextran, chitosan, cellulose, starch, gelatin, hyaluronic acid, and polymers or copolymers of the following monomers: N-(2-hydroxypropyl) methacrylamide, N-isopropylacrylamide, acrylamide, N,N-dimethylacrylamide, N-vinylpyrrolidone, vinyl acetate, 2-methacryloxyethyl glucoside, acrylic acid, methacrylic, vinyl phosphonic acid, styrene sulfonic acid, maleic acid, 2-methacryloxyethyltrimethylammonium chloride, methacrylamido-

propyltrimethylammonium chloride, methacryloylcholine methyl sulfate, N-methylolacrylamide, 2-hydroxy-3-methacryloxypropyltrimethyl ammonium chloride, 2-methacryloxyethyltrimethylammonium bromide, 2-vinyl-1-methylpyridinium bromide, 4-vinyl-1-methylpyridinium bromide, ethyleneimine, (N-acetyl)ethyl-eneimine, (N-hydroxyethyl)ethyleneimine, and allylamine. All of these polymers readily dissolve in water and are water-soluble polymers (hydrophilic polymers). In stark contrast, Woodle et al. describe using "vesicle-forming lipids" such as "amphipathic vesicle-forming lipids derivatized with a hydrophilic polymer" (see, e.g., column 3, lines 62-65). At columns 7-8, Woodle et al. define "vesicle-forming lipid" as "any amphipathic lipid having hydrophobic and polar head group moieties." Accordingly, the lipids of Woodle et al. are not water-soluble as they comprise water-**insoluble** hydrophobic regions. Indeed, the lipids of Woodle et al. do not dissolve in water, but rather form liposomes when introduced to water.

At pages 2-3 of the instant Official Action, the Examiner asserts that Woodle et al. teach a hydrophilic polymer (PEG) in combination with an anti-inflammatory agent at column 4, lines 32-50. Applicants respectfully disagree. The passage cited by the Examiner states that in a preferred embodiment, the hydrophilic biocompatible polymer is PEG. However, as explained in the preceding paragraph of Woodle et al., the hydrophilic biocompatible polymer is *linked* to a vesicle-forming lipid. Indeed, the vesicle-forming lipid is "derivatized" with the hydrophilic biocompatible polymer. Woodle et al. do not teach or suggest using the hydrophilic biocompatible polymer without conjugating it to a vesicle-forming lipid. The resultant copolymer of Woodle et al., therefore, comprises a hydrophilic polymer linked to an amphipathic lipid. The resultant copolymer is **not** a water-soluble polymer - as instantly claimed - as it necessarily has a hydrophobic (water **insoluble**) region in the lipid portion, as explained hereinabove.

Similarly, the "PEG liposomes" of Metselaar et al. are only PEG coated liposomes. Indeed, as explained at page 2060, the liposomes comprise a "PEG 2000-diasteroyl phosphatidyl ethanol amine (DSPE) conjugate", which is a PEG molecule conjugated to a lipid comprising a long hydrophobic chain. As such, the PEG-DSPE conjugate is not a water soluble polymer, as instantly claimed.

In view of the foregoing, it is evident that the references cited by the Examiner fail to teach or even suggest each and every element of the instantly claimed invention.

In addition to the above, the Examiner acknowledges at pages 3 and 4 of the instant Official Action that "neither Woodle et al. nor Metselaar et al. teach the PEG directly linked to the anti-inflammatory agent." Indeed, as explained above, the PEG molecules in Woodle et al. and Metselaar et al. are conjugated to lipids containing hydrophobic tails.

However, at page 4 of the instant Official Action, the Examiner alleges that it would have been "reasonable to link the drug and polymers directly to optimize therapeutic efficacy." Applicants respectfully disagree with the Examiner's position. At the outset, the Examiner states at page 4 of the Official Action that "one of ordinary skill in the art ... would have been motivated to directly link the anti-inflammatory drug to the carrier to ensure target delivery and accumulation at the inflamed areas." The Examiner cites page 2062 of Metselaar et al., but Metselaar et al. is void of any teaching or suggestion to directly link the anti-inflammatory to a polymer. Indeed, Woodle et al. and Metselaar et al. are clearly only describing formulations comprising a drug within a liposome. In stark contrast, the instant invention provides new "pro-drugs" wherein the drug is directly linked to the water-soluble polymer, thereby creating a new chemical entity. These new chemical entities were neither taught nor suggested by the references cited by the Examiner.

Moreover, the Examiner states at page 4 of the

instant Official Action that it would have been obvious to link "the anti-inflammatory drug to the carrier." In Metselaar et al., the "carrier" is the liposome which comprises the conjugate PEG-DSPE. As explained hereinabove, PEG-DSPE is clearly **not** a water-soluble polymer, as instantly claimed. Therefore, even using the reasoning provided at page 4 of the instant Official Action, one does still not arrive at the instantly claimed anti-inflammatory therapeutic agent linked to a water-soluble polymer.

It is also noteworthy that the anti-inflammatory agent is in the hydrophobic core of the liposomes of Woodle et al. and Metselaar et al. Moreover, the PEG is coated on the hydrophilic surface of the liposomes. Accordingly, the anti-inflammatory is not even in proximity to the PEG. Further, linking the anti-inflammatory to the PEG of the liposomes of Woodle et al. and Metselaar et al. would likely result in the anti-inflammatory being on the outside of the liposome and not in the core, as desired by Woodle et al. and Metselaar et al. (see below).

In addition to the above, Metselaar et al. and Woodle et al. teach away from using anything other than a liposome. Indeed, at page 2065, Metselaar et al. state that "liposomal encapsulation may not just enhance the concentration of drug at the target site, but also lower drug concentrations at non-target tissues." Metselaar et al. further add that prednisolone phosphate administered without liposomes was rapidly cleared and converted into a derivative. Therefore, it is without question that Metselaar et al. teach against using delivering an anti-inflammatory drug that is not entrapped or encapsulated within a liposome. Similarly, Woodle et al. only teach the use of liposomes, preferably those having "minimal leakage," as they effectively concentrate the therapeutic agent at the target site (see, e.g., column 19).

In view of all the foregoing, it is clear that Woodle et al. and Metselaar et al., considered alone or in

combination, fail to teach or suggest each and every element of the instantly claimed invention. Indeed, neither reference teaches a water-soluble polymer as instantly claimed nor the linking of a water-soluble polymer to an anti-inflammatory agent. In view of the foregoing, Applicants respectfully submit that the instant rejection is untenable. Withdrawal of the rejection is respectfully requested.

CLAIMS 2, 4, 6, 7, 9-14, AND 57-61 ARE NOT RENDERED OBVIOUS BY WOODLE ET AL. AND METSELAAR ET AL. IN VIEW OF OMELYANENKO ET AL. AND SMOLEN ET AL.

The Examiner has also rejected claims 2, 4, 6, 7, 9-14, and 57-61 under 35 U.S.C. §103(a) as allegedly unpatentable over Woodle et al. and Metselaar et al. in view of Omelyanenko et al. and Smolen et al. The Examiner acknowledges at page 4 of the instant Official Action that Woodle et al. and Metselaar et al. fail to teach an HPMA copolymer-drug conjugate, using cleavable or uncleavable linkers, using specific targeting moieties, using a plurality of therapeutic agents, and using a plurality of distinct bio-assay labels. The Examiner contends that Omelyanenko et al. teach conjugates using targetable HPMA copolymer linked to an anti-cancer drug by cleavable and non-cleavable linkers. Smolen et al. allegedly teach that the efficacy of rheumatoid arthritis therapy is enhanced by using combination therapies. It is the Examiner's position that it would have been obvious to a skilled artisan to combine these references to arrive at the instantly claimed invention. Applicants respectfully disagree with the Examiner's position.

At page 5 of the instant Official Action, the Examiner states that a skilled artisan "would have been motivated to substitute the HPMA copolymer carrier of Omelyanenko et al. for the PEG liposomes of Woodle et al. and Metselaar et al." Applicants respectfully disagree. As stated hereinabove, the instant claims recite anti-inflammatory therapeutic agents linked to a water-soluble

polymer. Further, Woodle et al. and Metselaar et al. describe liposomes entrapping or encapsulating anti-inflammatory NSAIDs and glucocorticoids, respectively. In contrast, Omelyanenko et al. is only concerned with the delivery of chemotherapeutic agents to cancer cells. Omelyanenko et al. also teach that polymer conjugated chemotherapeutic agents are more slowly delivered to cells than free drug. For example, at page 33, Omelyanenko et al. teach that free adriamycin, a DNA intercalator, intensely stain the nucleus within 30 minutes of exposure to HepG2 cancer cells. In contrast, "similar staining of nuclei with [adriamycin] was observed after **24 hour** incubation of HepG2 cells" with adriamycin conjugated to a polymer via a cleavable linker (emphasis added). Moreover, as explained at pages 34 and 35 of Omelyanenko et al., the proposed advantage of using HPMA-copolymer linked anti-cancer drugs is that the anti-cancer drugs "will be inaccessible" to the P-glycoprotein efflux pump, which confers multi-drug resistance to cancer cells. This advantage of HPMA copolymer conjugated anti-cancer drugs is relevant only to the treatment of cancer as *MRD1/P-glycoprotein* overexpression and efflux of anti-inflammatories is not a concern with the treatment of inflammation. In view of the foregoing, it is evident that Omelyanenko et al. teach that the conjugation of an anti-cancer drug to an HPMA-copolymer slows the delivery of the drug to its target. Moreover, the advantage provided by Omelyanenko et al. for using HPMA-copolymer conjugates is relevant to anti-cancer therapies and not anti-inflammatory therapies. Therefore, in contrast to the Examiner's assertion, the skilled artisan would **not** be motivated to substitute the HPMA copolymer carrier of Omelyanenko et al. for the PEG liposomes of Metselaar et al. and Woodle et al.

Additionally, as explained hereinabove, Metselaar et al. and Woodle et al. teach away from using anything other than a liposome for delivery of an anti-inflammatory. Indeed, Metselaar et al. and Woodle et al. are only concerned with vehicles for the drug and not modification of the drug or

generation of a pro-drug. At page 2065, Metselaar et al. state that, when comparing free drug to liposome encapsulated drug, "liposomal encapsulation may not just enhance the concentration of drug at the target site, but also lower drug concentrations at non-target tissues." Indeed, Metselaar et al. teach prednisolone phosphate administered without liposomes was rapidly cleared and converted into a derivative. Similarly, Woodle et al. only teach the use of liposomes, preferably those having "minimal leakage," as they effectively concentrate the therapeutic agent at the target site (see, e.g., column 19). These benefits observed by Metselaar et al. and Woodle et al. are, in part, due to the encapsulation of the drug within the liposomes. Omelyanenko et al. fail to teach or suggest that the anti-cancer drugs linked to the HPMA copolymers would be equally protected. Indeed, the experiments of Omelyanenko et al. are performed *in vitro*.

At page 4 of the instant Official Action, the Examiner also asserts that Omelyanenko et al. teach the use of a cleavable linker. However, as explained above, Omelyanenko et al. is concerned with the delivery of chemotherapeutic agents to cancer cells. There is no teaching or suggestion in the references cited by the Examiner that such linkages would be appropriate for the delivery of anti-inflammatory agents to inflammatory tissues. Moreover, Omelyanenko et al. fail to teach or suggest the pH sensitive hydrazone linker (new claim 67) of the instant invention. Indeed, the references cited by the Examiner fail to teach or suggest using acidosis in inflammation to trigger the anti-inflammatory prodrug activation.

Smolen et al. fail to supplement the deficiencies of the teachings of Metselaar et al., Woodle et al., and Omelyanenko et al. Indeed, Smolen et al. provide a review of therapeutic strategies for rheumatoid arthritis, but do not teach or suggest an anti-inflammatory therapeutic agent linked to a water-soluble polymer.

In view of all the foregoing, Applicants

respectfully submit that the instant rejection under 35 U.S.C. §103(a) is untenable. Withdrawal of the rejection is respectfully requested.

CLAIMS 1, 2, 4-15, AND 57-61 ARE NOT RENDERED OBVIOUS BY WANG ET AL. AND METSELAAR ET AL., OPTIONALY, IN VIEW OF SMOLEN ET AL. AND OMELYANENKO ET AL.

Claims 1, 2, and 4-15 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Wang et al. and Metselaar et al. The Examiner has also rejected claims 57-61 under 35 U.S.C. §103(a) as allegedly unpatentable over Wang et al. and Metselaar et al. in view of Smolen et al. and Omelyanenko et al. It is the Examiner's position that it would have been obvious to a skilled artisan to combine the teachings of Wang et al. and Metselaar et al. to arrive at the instantly claimed invention. Applicants respectfully disagree.

At page 6 of the instant Official Action, the Examiner alleges that Wang et al. teach water-soluble HPMA copolymer conjugates comprising bone-targeting compounds and the label FITC. The Examiner acknowledges that Wang et al. do not teach delivering therapeutic agents. Indeed, Wang et al. do not teach or suggest the administration of anti-inflammatory agents. Rather, Wang et al. discuss the delivery of bone therapeutic agents which promote the growth of bone (e.g., page 853, left column).

As explained hereinabove, Metselaar et al. teach away from using anything other than a liposome for delivery of an anti-inflammatory. Indeed, Metselaar et al. teach that liposomal encapsulation enhances the concentration of drug at the target site, lowers drug concentrations at non-target tissues, and prevents degradation and clearance of the encapsulated drug. Metselaar et al. conclude at page 2066, that the encapsulation of the anti-inflammatory in PEG liposomes leads to the "enhanced and preferential localization of the drug in the inflamed joints." Absent the encapsulation

in the liposomes, Metselaar et al. teach that the administration of free anti-inflammatory drug is not effective and leads to the degradation of the drug (page 2065). Therefore, Metselaar et al. teach against using an anti-inflammatory drug in the absence of a liposome.

At page 6 of the instant Official Action, the Examiner also asserts that Wang et al. teach the use of a cleavable linker. However, as explained above, Wang et al. is concerned with the delivery of bone therapeutic agents which promote the growth of bone. There is no teaching or suggestion in the references cited by the Examiner that such linkages would be appropriate for the delivery of anti-inflammatory agents to inflammatory tissues. Moreover, Wang et al. fail to teach or suggest the pH sensitive hydrazone linker (new claim 67) of the instant invention. Indeed, the references cited by the Examiner fail to teach or suggest using acidosis in inflammation to trigger the anti-inflammatory prodrug activation.

Moreover, Applicants submit that the combination of Metselaar et al. and Wang et al. does not suggest and, in fact, teaches away from the targeting of anti-inflammatory agents to bone or cartilage, as asserted by the Examiner at page 7 of the instant Official Action. As stated hereinabove, Wang et al. only reference the delivery of bone therapeutic agents which promote the growth of bone and only actually link the detectable agent FITC to the HPMA copolymer. Metselaar et al. also fail to teach or suggest using any bone or cartilage targeting moiety to deliver an anti-inflammatory agent. Rather, Metselaar et al. teach that the PEG conjugates within the liposomes are sufficient to target the liposomes to inflammatory tissue (see, e.g., pages 2060 and 2062). Metselaar et al. "stress" the importance of increasing circulation time in order to increase joint localization (page 2065). Notably, Wang et al. clearly teach that the epiphysis (rounded ends of long bones) and diaphysis (main section or shaft of long bones) were labeled by the bone-targeting

conjugates (page 857). Thus, Wang et al. expressly teach that the bone-targeting conjugates bind bone outside of joints. Inasmuch as Metselaar et al. teach that the PEG liposomes already target inflammatory tissue, a skilled artisan would avoid adding the bone targeting moiety of Wang et al. because the bone targeting moiety may bind to other, more abundant, regions of bone, such as the diaphysis of the femur and any other long bones, thereby drawing the PEG liposomes away from the site of inflammation. However, the instant application demonstrates unexpectedly superior results in that the intravenous administration of the instantly claimed compositions targeted the site of inflammation in the host (e.g., in the rat ankle) and effectively delivered the anti-inflammatory drug to treat the inflammation.

In view of the foregoing, Applicants submit that the skilled artisan would have neither the motivation nor the expectation of success in combining the teachings of Metselaar et al. and Wang et al. to arrive at the instantly claimed invention.

As to the rejection of claim 57-61, the Examiner has further cited Smolen et al. and Omelyanenko et al. For the reasons set forth above regarding Wang et al. and Metselaar et al., the instant rejection is untenable. Moreover, as explained hereinabove, Smolen et al. do not teach or suggest an anti-inflammatory therapeutic agent linked to a water-soluble polymer. Indeed, Smolen et al. is largely a review of various therapeutic drugs and methods for the treatment of rheumatoid arthritis, but does not specifically teach or suggest the carriers of the instant invention.

Further, Omelyanenko et al. is only concerned with the delivery of chemotherapeutic agents to cancer cells. As explained above, Omelyanenko et al. actually demonstrate that polymer conjugated chemotherapeutic agents are more slowly delivered to cells than free drug. Moreover, as explained at pages 34 and 35 of Omelyanenko et al., the proposed advantage of using HPMA-copolymer linked anti-cancer drugs is that the

anti-cancer drugs "will be inaccessible" to the P-glycoprotein efflux pump, which confers multi-drug resistance to cancer cells. This advantage of HPMA copolymer conjugated anti-cancer drugs is relevant only to the treatment of cancer as MRD1/P-glycoprotein overexpression and efflux of anti-inflammatories is not a concern with inflammation.

In view of the foregoing, it is evident that Omelyanenko et al. and Smolen et al. fail to supplement the deficiencies of Wang et al. and Metselaar et al.

In light of all the foregoing, Applicants respectfully submit that the instant rejections under 35 U.S.C. §103(a) cannot be reasonably maintained. Withdrawal of the rejections is respectfully requested.

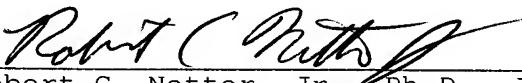
CONCLUSION

In view of the foregoing remarks, it is respectfully urged that the rejections set forth in the December 21, 2010 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below.

Respectfully submitted,
DANN, DORFMAN, HERRELL AND SKILLMAN
A Professional Corporation

By



Robert C. Netter, Jr., Ph.D., J.D.
PTO Registration No. 56,422

Telephone: (215) 563-4100
Facsimile: (215) 563-4044